UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF TEXAS
WACO DIVISION

Zanoprima Lifesciences Ltd., Plaintiff, v. Hangsen International Group Ltd., Defendant.	Case No. 6:22-cv-00268-ADA

HANGSEN'S REPLY SUPPORTING MOTION FOR SUMMARY JUDGMENT OF NO ENABLEMENT AND INSUFFICIENT WRITTEN DESCRIPTION

Hangsen submits this reply brief in support of its motion for summary judgment that all claims of the Asserted Patent are invalid for lacking enablement and written description support.

I. THE ASSERTED PATENT LACKS SUFFICIENT WRITTEN DESCRIPTION

Zanoprima's opposition brief confirms that the Asserted Patent is invalid for lack of written description under 35 U.S.C. § 112(a). Each Asserted Patent claim requires "an enzyme with imine reductase activity." (ECF No. 80-1 at 19:59–20:59.) Zanoprima does not dispute that "more than a thousand" such enzymes exist. (ECF No. 81 at 15) (quoting Juan Mangas-Sanchez, *Imine Reductases (IREDs)*, 37 Current Opinion in Chemical Biology, at 19–25 (Apr. 2017)). And Zanoprima concedes that the Asserted Patent mentions only "several" such enzymes. (ECF No. 83 at 12.) Zanoprima calls them "working examples" (*id.*), but "several" "working examples" alone do not provide enough written description support for a claim reciting an entire genus of enzymes. Rather, the Asserted Patent must either: (1) identify "common structural features" between the example enzymes and all the other enzymes in the genus, or (2) explain how the examples are "representative" of all the enzymes in the genus. *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1342 (Fed. Cir. 2021). The Asserted Patent does neither.

First, Zanoprima does not identify "common structural features" anywhere in its brief. Zanoprima has thereby waived any argument based on common structural features. *See DirecTV Inc. v. Forman*, 126 F. App'x 676, 677 (5th Cir. 2005). And even if Zanoprima had not waived it, such an argument would still fail. In its answer to an interrogatory about structural features, Zanoprima contends that "enzymes with imine reductase activity *are* NAD(H)/NADP(H) dependent oxidoreductases." (ECF No. 83-9 at 6) (emphasis added). But Zanoprima's contention is inconsistent with the Asserted Patent itself, which says that "enzymes with imine reductase activity typically *include* NADH/NADPH dependent oxidoreductases." (ECF No. 80-1 at 3:52–53) (emphasis added). "[T]he word 'include[]' is open-ended and permits more than that which follows." *Good Tech. Corp. v. MobileIron, Inc.*, No. 5:12-CV-05826, 2015 WL 3980940, at *9 & n.87 (N.D. Cal. June 30, 2015) (citing *Hewlett-Packard Co. v. Repeat-O-Type Stencil Mfg. Corp.*, 123 F.3d 1445, 1451 (Fed. Cir. 1997)). In other words, the Asserted Patent's specification admits that it covers additional enzymes beyond the NAD(H)/NADP(H) dependent oxidoreductases named in Zanoprima's interrogatory answer. Yet the Asserted Patent says nothing about those additional enzymes' structural features. Zanoprima's interrogatory answer "could not overcome[]" this "admission[] in the specification," even if Zanoprima had cited the answer in its opposition brief. *CareDx, Inc. v. Natera, Inc.*, 40 F.4th 1371, 1377 (Fed. Cir. 2022).

Second, Zanoprima does not contend that the "several" working-example enzymes are representative of all enzymes with imine reductase activity claimed in the Asserted Patent. Since May 2023, Zanoprima's interrogatory answers have expressly *disclaimed* representativeness:

> Zanoprima does not contend that the enzymes identified in the examples of the '962 Patent are representative of all enzymes with imine reductase activity. Zanoprima contends that the disclosures regarding enzymes with imine reductase activity in the '962 Patent are sufficient to enable a person of ordinary skill in the art to practice the claimed processes of the '962 Patent.

(ECF No. 81-2 at 7) (emphasis added). Yet just last week, while this motion was pending, Zanoprima "amended" its interrogatory answers to claim the exact opposite—that the example enzymes actually *were* representative:

> Zanoprima contends that the enzymes identified in the examples of the '962 Patent are representative of enzymes with imine reductase activity that may be used to stereoselectively reduce myosmine to (S)-nornicotine.

(ECF No. 83-9 at 5) (emphasis added).[1] This conveniently timed "amendment" must be disregarded.

Zanoprima cannot avoid summary judgment by reversing its interrogatory answers at the last moment. "[A] nonmoving party may not manufacture a dispute of fact merely to defeat a motion for summary judgment." *Doe ex rel. Doe v. Dallas Indep. Sch. Dist.*, 220 F.3d 380, 386 (5th Cir. 2000).[2] For example, a nonmoving party cannot "materially change its interrogatory response after receiving a summary judgment motion in an attempt to defeat that motion." *Wleklinski v. Targus, Inc.*, No. 05-1143, 2007 WL 9711249, at *4 (C.D. Cal. Mar. 16, 2007), *aff'd*, 258 F. App'x 325 (Fed. Cir. 2007); *see also Margo v. Weiss*, 213 F.3d 55, 60–61 (2d Cir. 2000) ("[P]laintiffs cannot defeat a motion for summary judgment . . . by filing 'supplemental answers' to interrogatories."). Such a "self-serving, suspect" amended interrogatory answer is "insufficient

[1] Zanoprima's addition of the words "that may be used to stereoselectively reduce myosmine to (S)-nornicotine" is redundant. Hangsen's interrogatory asked for Zanoprima's contentions about "Claimed Enzymes," which Hangsen defined by the relevant patent claim language: "enzyme[s] with imine reductase activity that [are] capable of reducing myosmine to form (S)-nornicotine." *See* Ex. 9 at 1; ECF No. 80-1 at cl. 1. Each set of Hangsen's interrogatories, and each set of Zanoprima's answers, thus incorporates the concept of stereoselectively reducing myosmine to (S)-nornicotine.

[2] Because these "issues relating to district court summary judgment procedures" do not "affect[] substantive patent law principles," Fifth Circuit law controls. *In re Cygnus Telecomm. Tech., LLC, Pat. Litig.*, 536 F.3d 1343, 1351–52 (Fed. Cir. 2008).

to raise a genuine issue of material fact." *Reese v. AT & T Mobility II, LLC*, No. 2:13-CV-05198, 2014 WL 1873046, at *4 (C.D. Cal. May 9, 2014). Zanoprima's original answer to the interrogatory thus controls, and it confirms that "the enzymes identified as examples [in] the '962 Patent" are *not* "representative of all enzymes with imine reductase activity." (ECF No. 81-2 at 7.)

In any event, Zanoprima's "amended" answer does not save it from summary judgment. That answer, like the expert testimony allegedly supporting it, is conclusory. "[C]onclusory allegations in . . . answers to . . . interrogatories" are "insufficient to defeat a motion for summary judgment." *Grace v. Keystone Shipping Co.*, 805 F. Supp. 436, 444 (E.D. Tex. 1992) (citing *Orthopedic & Sports Injury Clinic v. Wang Lab'ys, Inc.*, 922 F.2d 220, 225 (5th Cir. 1991)). Similarly, "the mere conclusory allegations of [an] expert witness are not competent summary judgment evidence" and "are therefore insufficient to defeat . . . a motion for summary judgment." *Meade v. Dillard Dep't Stores*, 275 F.3d 43, 2001 WL 1223752, at *5 (5th Cir. Oct. 4, 2001) (quotation omitted). Zanoprima offers nothing more than these types of insufficient evidence.

In its opposition brief, Zanoprima makes two primary—and conclusory—arguments for representativeness:

1. "[A] POSITA would readily recognize that the inventors had practiced the two claimed steps of the process and synthesized (S)-nicotine using those working examples of enzymes with imine reductase activity." (ECF No. 83 at 13) (citing ECF No. 83-1 ¶ 36).

2. "[T]he working examples in the '962 Patent are representative of enzymes with imine reductase activity . . . ." (*Id.*) (citing ECF No. 83-1 ¶ 37).

These conclusory arguments cite only two paragraphs of Zanoprima's expert declaration. (*See id.*) (citing ECF No. 83-1 ¶¶ 36, 37). Those two paragraphs contain the same conclusory statements that Zanoprima makes in its brief. (*See* ECF No. 83-1 ¶¶ 36, 37.) They all should be disregarded.

The closest Zanoprima comes to a non-conclusory statement is its allegation that two "working examples" of claimed enzymes, called IRED_A and IRED_B, "have 33% sequence

homology and belong to different superfamilies, yet both exhibit high selectivity for myosmine." (ECF No. 83 at 13; ECF No. 83-1 ¶ 37.) "[T]hese working examples," according to Zanoprima, are therefore "representative of enzymes with imine reductase activity." (ECF No. 83-1 ¶ 37.) Even if true, that would not show representativeness. It is not enough for Zanoprima to identify two example enzymes that "achieve the claimed function" of high selectivity for myosmine. *Juno*, 10 F.4th at 1342. Zanoprima's examples must "allow a person of ordinary skill in the art to distinguish between" enzymes "that achieve the claimed function" and enzymes "that do not." *Id.* Zanoprima's examples, however, raise more questions than answers: if two enzymes that are only 33% similar to each other could each "exhibit high selectivity for myosmine," then how could a person of ordinary skill in the art distinguish them from enzymes that do *not* exhibit high selectivity for myosmine? Zanoprima does not say. This is yet another reason why the Court should hold the Asserted Patent invalid for lack of written description and should grant Hangsen's motion for summary judgment.

II. THE CLAIMS OF THE ASSERTED PATENT ARE NOT ENABLED

Zanoprima's Asserted Patent claims lack enablement. Zanoprima mischaracterizes the claims, overstates what the Asserted Patent's specification discloses, and misapplies binding law.

A. Zanoprima Mischaracterizes the Breadth of Its Claims and Reads Terms Out of Context.

Zanoprima's opposition relies heavily on reading the term "enzyme with imine reductase activity" out of context from the rest of the claim. The first step in claim 1 reads as follows: "(i) reducing myosmine with an enzyme with imine reductase activity to form (S)-nornicotine." While Zanoprima argues that "[t]he '962 Patent does not broadly claim enzymes," it cannot be disputed that it claims a process covering the use of every enzyme that reduces myosmine to form (S)-nornicotine in the context of synthesizing (S)-nicotine. The Court confirmed this

understanding, construing the term "enzyme with imine reductase activity to form (S)-nornicotine" as "enzyme capable of stereoselectively reducing an imine group to form more (S)-nornicotine than (R)-nornicotine." (ECF No. 54 at 2.)

Stated another way, claim 1 covers a genus of processes of synthesizing (S)-nicotine that include a step of reducing myosmine using an enzyme with imine reductase activity to form (S)-nornicotine, with each use of a distinct enzyme to reduce myosmine to form (S)-nornicotine being a separate species within the claimed genus. Reducing myosmine with IRED_A to form (S)-nornicotine is one species. Reducing myosmine with IRED_C to form (S)-nornicotine is another species. Reducing myosmine with IRED_AB to form (S)-nornicotine is another species—and so on, potentially many thousands of times over. The Asserted Patent covers them all, provided that the claimed "enzyme with imine reductase activity" succeeds in reducing myosmine "to form more (S)-nornicotine than (R)-nornicotine." So the Asserted Patent *does* "broadly claim enzymes."

B. Zanoprima Overstates the Disclosure of the Specification

Zanoprima argues that the Asserted Patent "discloses nine different, commercially available, imine reductases." (ECF No. 83 at 6.) This misstates the disclosure. Stating that an enzyme has been given an arbitrary codename like IRED_C and was used in activity and enantiomeric excess experiments does not disclose the enzyme such that a person of ordinary skill can make and use it. Zanoprima does not dispute, because it cannot, that the Asserted Patent does not disclose the sequence, structure, host organism, or anything else that would enable a skilled person to know specifically what enzyme each of IRED_C, IRED_D, IRED_E, IRED_F, IRED_P, IRED_X, and IRED_AB is. Instead, as Zanoprima admits, the Asserted Patent "discloses full protein sequences" for only "two of those enzymes with imine reductase activity—IRED A and IRED B." (*Id.*; *see also* ECF No. 81 at 14 (noting that "the specification discloses just two enzyme sequences: those of IRED_A and IRED_B").)

Unable to point to any teaching in the Asserted Patent about how to identify enzymes other than IRED_A or IRED_B, Zanoprima trivializes the problem. Zanoprima argues that a skilled person "could have identified such other enzymes by using known classifications of enzymes and routine screening techniques." (ECF No. 83 at 7.) That is, Zanoprima says that other enzymes could be identified using rote, trial-and-error screening of enzymes—weeding out those enzymes that act on myosmine to form more (S)-nornicotine than (R)-nornicotine from the more than 63,000 known candidates. In fact, Zanoprima itself called enzyme screening "nothing more than a process of trial and error." Ex. 8 at 15. That is the opposite of enablement. "[R]andom trial-and-error discovery" without identifying "a quality common to every functional embodiment"—as Zanoprima proposes in its opposition—"is not enablement." *Amgen Inc. v. Sanofi*, 143 S. Ct. 1243, 1256–57 (2023).

C. Zanoprima Misapplies the Law on Enablement

Zanoprima argues that *Amgen* does not apply to the claims of the Asserted Patent, attempting to limit *Amgen* to claims directed to a genus of enzymes instead of claims directed to a genus of processes recited by broadly claiming a genus of enzymes to perform the process. To be clear, the claims of the Asserted Patent, structured as process claims, cover the use of every enzyme that reduces myosmine to form (S)-nornicotine in the context of synthesizing (S)-nicotine.

Contrary to Zanoprima's argument, *Amgen* expressly applies, as the Supreme Court stated:

> Our decisions in *Morse*, *Incandescent Lamp*, and *Holland Furniture* reinforce the simple statutory command. ***If a patent claims an entire class of processes***, machines, manufactures, or compositions of matter, ***the patent's specification must enable a person skilled in the art to make and use the entire class***. In other words, the specification must enable the full scope of the invention as defined by its claims. The more one claims, the more one must enable.

Id. at 1254 (emphasis added). The patent claims that the Supreme Court confirmed were not enabled in *Amgen* had claims that broadly covered "all antibodies that (1) bind to specific amino

acids on a naturally occurring protein known as PCSK9, and (2) block PCSK9 from impairing the body's mechanism for removing LDL cholesterol from the bloodstream." *Id.* at 1248. Similarly here, the Asserted Patent broadly covers the genus of processes for synthesizing (S)-nicotine that include a step of "reducing myosmine using an enzyme with imine reductase activity to form (S)-nornicotine," with each use of a distinct enzyme to reduce myosmine to form (S)-nornicotine being a separate species within the claimed genus. Both the claims in *Amgen* and the claims here recite a genus defined by a class of proteins recited not by structure or sequence, but by function.

Just like the patents invalidated in *Amgen*, the size of the genus potentially claimed by the Asserted Patent is very large. Using the classes of enzymes disclosed in the specification—"NADH/NADPH dependent dehydrogenases" and "NADH/NADPH dependent imine reductases" (ECF No. 80-1 at 3:51-55)—there are at least 63,367 known NADH/NADPH dependent dehydrogenases and over 1,400 known NADH/NADPH dependent imine reductases. (ECF No. 81-1 ¶¶ 26, 38.) And Zanoprima notably ignores—it is thus undisputed—that the true number of potential enzymes is "exponentially higher" when accounting for selective mutation through enzyme engineering. (*Id*. ¶ 41.) But even if a skilled person were to consider only NADH/NADPH dependent imine reductases (ignoring the broader statement of the Asserted Patent that "enzymes with imine reductase activity typically include NADH/NADPH dependent oxidoreductases, such as NADH/NADPH dependent dehydrogenases, and NADH/NADPH dependent imine reductases"), and were to further limit the class to one database that identified over 1,400 distinct imine reductase sequences, and still further were to ignore the undisputed realities of enzyme engineering, that potentially claimed class is still poles apart from what the specification actually disclosed. At the end, Zanoprima cannot overcome that its patent discloses just two enzymes, IRED_A and IRED_B, in any detail, yet broadly claims a genus of processes for synthesizing (S)-

nicotine using any enzyme with imine reductase activity that reduces myosmine to form more (S)-nornicotine than (R)-nornicotine.

Just like the *Amgen* patents, Zanoprima's specification contains no disclosure about any common sequence feature or any common structural characteristic in the two disclosed enzymes that would allow a skilled person to identify "a quality common to every functional embodiment." *Amgen*, 143 S. Ct. at 1256. And while Zanoprima offers the conclusory argument that the two disclosed enzymes are "representative," both it and its expert omit any discussion about why or how they are representative, point to no specific sequence commonality that other claimed enzymes would share, and fail to identify what structural feature those enzymes and others capable of reducing myosmine to form more (S)-nornicotine than (R)-nornicotine have in common that "gives [them] 'a peculiar fitness for the particular purpose.'" *Id*. at 1254–55 (quoting *Consol. Elec. Light Co. v. McKeesport Light Co.*, 159 U.S. 465, 475 (1895)).

With respect to whether the specification teaches a skilled person how to discover other examples, the Asserted Patent implies only that a skilled person could obtain a small number of enzymes commercially. It provides no teaching about how to discover others. And Zanoprima's suggestion for how to discover others—screening—is exactly the activity that the Supreme Court found to be undue, trial-and error experimentation:

> These two approaches [disclosed in the specification] amount to little more than two research assignments. The first merely describes step-by-step Amgen's own ***trial-and-error method*** for finding functional antibodies—***calling on scientists to create a wide range of candidate antibodies and then screen each*** to see which happen to bind to PCSK9 in the right place and block it from binding to LDL receptors. . . . The second isn't much different. It requires scientists to make substitutions to the amino acid sequences of antibodies known to work and then test the resulting antibodies to see if they do too.

Amgen, 143 S. Ct. at 1256 (emphasis added). Even Zanoprima admits that enzyme screening is "nothing more than a process of trial and error." Ex. 8 at 15.

Additionally, like the art in *Amgen* (involving antibody proteins), the art here (involving enzyme proteins) is unpredictable. Zanoprima does not dispute this. Nor does it dispute the fact that changing just one or two amino acids in an enzyme could unpredictably change its function, requiring experimental testing to determine if the change affected the enzyme's function and, if so, to what extent. (*See* ECF No. 83 at 14.) Zanoprima argues that this fact "misses the point" because the specification "discloses at least two commercially available enzymes that would predictably enable a person of ordinary skill in the art to practice the full scope of the claimed process." (*Id*.) Yet it is Zanoprima that misses the mark. The Asserted Patent claims not just one process, but a whole genus of processes claimed by broadly reciting a genus of enzymes that function to perform the process. The disclosure of IRED_A and IRED_B—the only enzymes enabled by the specification—informs the skilled person of just two species of the claimed genus. A skilled person may know how to make synthetic (S)-nicotine by (1) reducing myosmine using IRED_A to form (S)-nornicotine and (2) reducing myosmine using IRED_B to form (S)-nornicotine. But the claims cover all other syntheses of (S)-nicotine involving the reduction of myosmine using any other enzyme with imine reductase activity to form more (S)-nornicotine than (R)-nornicotine, and nothing else in that broad scope is enabled.

Finally, Zanoprima falsely argues that Hangsen failed to address the issue of undue experimentation. But the points discussed above are all factors relevant to undue experimentation and, importantly, follow the Supreme Court's most recent analysis of enablement in a highly analogous art.

III. CONCLUSION

The Court should grant Hangsen's motion for summary judgment and find that all claims of the Asserted Patent are invalid as not enabled and lacking written description support.

Date: August 10, 2023

Respectfully submitted,

/s/ Kevin W. Kirsch

Deron R. Dacus (Bar No. 00790553)
ddacus@dacusfirm.com
THE DACUS FIRM, P.C.
821 ESE Loop 323, Suite 430
Tyler, TX 75701
Telephone: (903) 705-1117
Facsimile: (903) 581-2543

Kevin W. Kirsch (Bar No. 81996)
kkirsch@bakerlaw.com
Andrew E. Samuels (admitted *pro hac vice*)
asamuels@bakerlaw.com
BAKER & HOSTETLER LLP
200 Civic Center Drive, Suite 1200
Columbus, OH 43215
Telephone: (614) 228-1541
Facsimile: (614) 462-2616

Kevin P. Flynn (admitted *pro hac vice*)
kflynn@bakerlaw.com
BAKER & HOSTETLER LLP
312 Walnut Street, Suite 3200
Cincinnati, OH 45202
Telephone: (513) 929-3400
Facsimile: (513) 929-0303

Attorneys for Defendant
Hangsen International Group Ltd.

CERTIFICATE OF SERVICE

I certify that on August 10, 2023, I served the foregoing document via the CM/ECF system on:

Jaime Stark (jaime.stark@nortonrosefulbright.com)
Daniel A. Prati (daniel.prati@nortonrosefulbright.com)
Marc B. Collier (marc.collier@nortonrosefulbright.com)

Attorneys for Plaintiff Zanoprima Lifesciences, Ltd.

/s/ Kevin W. Kirsch
Kevin W. Kirsch